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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,209	ADLER, JON ELLIOT	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *138-185* is/are pending in the application.

4a) Of the above claim(s) *175 and 177-185* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *138-174 and 176* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *none* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 2/28/2005, have been entered in full.

Claims 175, 177-185 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant's election of the species of SEQ ID NO: 3 and 4 (T2R54) in the Paper received 9/01/2006, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

The information disclosure statement filed 3/16/2004 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 17 and 37 for example. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 138-174 and 176 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 138, and dependent claims require a compound that "putatively" enhances, inhibits, or elicits bitter taste. It is unclear what limitations Applicant intends the world putatively to add to the claims, and nor is such explained in the specification. Thus, an artisan could not be sure whether he or she was practicing or infringing on Applicant's claims.

Claims 138 and 141 require that the nucleic acid hybridize under stringent conditions. The term stringent conditions is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. The term appears to be defined only by way of

example at page 31. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, e.g., salt concentration and temperature conditions of incubations and washes.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 138-174 and 176 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 138(2) is worded such that the claim literary requires that the receptor be in a state of activation or capable of activation during the step of "identifying a compound... based on its effect on the activation of at least one T2R polypeptide...". One skilled in the art would thus understand that one would need to be able to produce a state of activation of the receptor either before, during, or after the step of contacting the receptor with the compound in order to accomplish the goal of identifying a compound based on its effect on the activation of at least one T2R polypeptide. The specification asserts that the instant hT2R54 polypeptide (SEQ ID NO: 4) is a bitter taste receptor, however the specification does not teach which of the thousands of different and structurally unrelated compounds that can be perceived by humans as bitter can actually be used to activate the hT2R54. In the parent Application 09825882, evidence was

provided that after screening a specially developed library of 15,000 potential bitter tastant compounds, the inventors eventually discovered only a single compound, nitrosaccharin, that effectively activated the hT2R61 polypeptide (SEQ ID NO: 8) see Applicant's response of 5/14/2004 in the 09825882 Application. No specific teaching is provided for the instant hT2R54 as to what might activate it and nor is there any mention of the specially developed library referred to above. It is noted that in Applicant's reply of 9/1/2006, it is asserted that hT2R54 specifically responds to acetaminophen and that functional data will be provided later in the form of a Declaration. First however, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37; *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). Second, the instant specification says nothing about acetaminophen, and incorporation of such would constitute new matter.

Assuming that the claims can be reworded such that receptor activity need only be measured but not necessarily produced or inhibited, i.e., in screening for agonists of the receptor, the instant claims 138, 141, 142, 145-174, 176 are directed to a genus of variants of SEQ ID NO: 4 that are not enabled. Claims 138, 141, 142, 145-174, 176 encompass a genus of polypeptide variants of the polypeptide of SEQ ID NO: 4 i.e. substitutions, deletions or insertions in a protein

corresponding to SEQ ID NO: 4 or comprising only "functional fragments" of SEQ ID NO: 4 Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not at least 95% identical to the polypeptide of SEQ ID NO: 4 (see the 09825882 Application), but which still retain a desired property of the polypeptide of SEQ ID NO: 4. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 4 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 4 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 4, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 4.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional

spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract.

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 4 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created. Further, claim 138(b) encompasses all polypeptides comprising an amino acid sequence of (a); this includes

polypeptides with as little as two amino acids in common with (a), and differing entirely in the rest of the sequence. It is suggested that replacing the word "an" in (a) with "the" would obviate this aspect of the rejection.

The problem of producing active variants appears especially difficult in the art of T2R receptors, to which the instant polypeptide is asserted to belong. The instant specification appears to simply suggest to the artisan that art-recognized procedures for screening GPCRs (e.g. pages 50-63) are sufficient to identify functional variants of SEQ ID NO: 4 However, Hoon *et al., Cell* 96(541-551)1999, report that "We have attempted to determine the ligand/tastant specificity of TR1 and TR2 using a variety of strategies but have been hampered by the difficulty of functionally expressing these molecules in heterologous systems" see col 1 of page 547. Further, Chandrashekar et al., Cell 100(703-711)2000 reported that they were able to record a response from only 1 of the 11 human T2R clones tested, see col 1 of page 707. Thus, the art regarding T2R receptors, as exemplified by Hoon et al., and Chandrashekar et al, recognizes the complexity, unpredictability, and non-routine nature of the work involved in trying to assay functional T2R receptors. The instant specification has provided only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such a screening method.

The specification has also failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 3, e.g. no disorder or phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might now where to obtain a variant. The specification merely offers the skilled artisan the invitation to randomly try to find variants

through trial and error sampling of animal populations. The instant specification has provided only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such a screening method. While, it may be reasonable that the instant specification is enabling for variants that are at least 95% identical to SEQ ID NO: 4, see parent Application 09825882, the scope of the instant claims is vastly wider than such and does not appear to be supported by and adequate disclosure.

Due to the large quantity of experimentation necessary to generate the essentially infinite number of variants recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the difficulties encountered in screening T2Rs, exemplified by Hoon et al. and Chandrashekar et al., and the breadth of the claims which fail to recite adequate structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 138-174 and 176 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As discussed above, claim 138(2) is worded such that the claim literary requires that the receptor be in a state of activation or capable of activation during the step of "identifying a compound... based on its effect on the activation of at least one T2R polypeptide...". One skilled in the art would thus understand that one would need to be in possession of a compound or method for producing a state of activation of the receptor either before, during, or after the step of contacting the receptor with the compound in order to accomplish the goal of identifying a compound based on its effect on the activation of at least one T2R polypeptide. The specification, as filed, does not provide any means for accomplishing this, and thus the skilled artisan would not recognize that Applicant was in possession of the claimed invention at the time of filing.

Additionally, the specification discloses a cDNA polynucleotide of SEQ ID NO: 3 encoding a polypeptide of SEQ ID NO: 8, yet the claims encompass the use of polypeptide variants not described in the specification, e.g. mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 3, encoding a polypeptide that binds a single ligand, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli*

Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide of SEQ ID NO: 3, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

The specification has not provided a particular essential feature, either a functional or structural feature, that the claimed genus of polynucleotides possess. The recitation of the property of hybridization does not, alone, provide sufficient information regarding the structure of the polynucleotide variants. Further, most of these variants are expected to encode polypeptides having an amino acid sequence different than that of SEQ ID NO: 4 and thus having different structural and functional properties. Similarly, the recitation of a percent identity to SEQ ID NO: 4 provides no description of any amino acid sequence other that of SEQ ID NO: 8. The specification has not defined what particular common structural or functional properties are possessed by the claimed genus of polynucleotides. Thus one of skill in the art would appreciate that Applicant was not in possession of the claimed genus of assay methods using variants of SEQ ID NO: 4.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

November 11, 2006

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SUPERVISORY PATENT EXAMINER
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